

R E M A R K S

The Examiner is respectfully requested to acknowledge receipt of the certified copies of the priority documents that were filed on August 20, 2001.

With respect to Rule 116, entry of the amendments is respectfully requested since the amendments do not involve the inclusion of any new features that were not previously set forth in the claims prior to the final rejection, and the amendments are in response to the paragraph bridging pages 4 and 5 of the final rejection.

The Office Action enclosed copies of the INFORMATION DISCLOSURE STATEMENT BY APPLICANT Form PTO/SB/08A dated December 3, 2002 and the Forms PTO/SB/08A and PTO/SB/08B dated June 20, 2003, with the Examiner's initials in the left column next to each cited publication.

Next to the citations of JP 59-210871 and JP 60-094075 at the bottom of the copy of the December 3, 2002 Form PTO/SB/08A that was returned with the Office Action, the Examiner made a handwritten notation of "ABS only". It is considered that "ABS" means "Abstract". It is respectfully submitted that no notation should have been placed next to the initialed publications on the

aforesaid copy of the December 3, 2002 Form PTO/SB/08A, based on the following statement on page 600-132 (in Section 609) of the MPEP:

"The examiner should not require that a translation be filed by applicant. The examiner should not make any comment such as that the non-English language information has only been considered to the extent understood, since this fact is inherent."

JP 59-210871 and JP 60-094075 were cited in the European Search Report of the corresponding European application. This satisfies the statement of relevance required by the Patent Office Rules. See page 630-122 in Section 609 of the MPEP which states as follows:

"Where the information listed is not in the English language, but was cited in a search report or other action by a foreign patent office in a counter-part foreign application, the requirement for a concise explanation of relevance can be satisfied by submitting an English-language version of the search report or action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an 'X', 'Y', or 'A' indications on a search report."

In view of the above, it is respectfully submitted that the Examiner's notation of "ABS" next to these two publications is not appropriate.

Applicants have provided the following comments concerning JP 59-210871 and JP 60-094075. Applicants fully reviewed the two Japanese-language publications and found that there is no mention of anserine, dipeptides, D-ribose or any of the related substances for anti-fatigue composition in these publications. Instead, the publications deal only with selected amino acids, histidine, lysine, arginine, leucine, isoleucine and valine in combination with vitamin E and either sodium ions or calcium ions.

The Examiner is therefore respectfully requested to return another initialed copy of said Form PTO/SB/08A dated December 3, 2002, without any notations thereon.

The presently claimed invention concerns a muscular fatigue-controlling composition which comprises a muscular fatigue-controlling effective amount of (a) an imidazole compound which is anserine or a salt thereof and (b) D-ribose, as active ingredients, in combination with an excipient.

The presently claimed invention also is directed to a method for providing a muscular fatigue-controlling effect comprising

orally administering to a person in need thereof a muscular fatigue-controlling effective amount of a muscular fatigue-controlling composition which comprises (a) an imidazole compound which is anserine or a salt thereof and (b) D-ribose, as active ingredients.

Claims 1, 3, 5 to 7, 9, 11 to 16 and 20 to 21 were rejected under 35 USC 103 as being unpatentable over Harris et al. USP 5,965,596 in view of St. Cyr et al. USP 6,159,942 for the reasons set forth at the bottom of page 2 and continuing to the bottom of page 3 of the Office Action.

It was admitted in the Office Action that Harris et al. do not teach the inclusion of ribose.

The method disclosed in Harris et al. is directed to administering beta-alanine along with L-histidine and/or creatine, orally or by injection, to increase the content of beta-alanine alone or to increase the content of beta-alanine with L-histidine and/or creatine in blood plasma, thereby increasing the synthesis of beta-alanylhistidine dipeptide and creatine. Namely, Harris et al. disclose increasing the anaerobic working capacity of muscles and other tissues by increasing the beta-alanylhistidine content in blood plasma.

At the top of page 3 of the Office Action, the following is stated:

"Harris teaches administration of chicken broth, which contains anserine and carnosine, to subjects (example 2). Harris et al. teaches the additional use of creatine and carbohydrates, such as sugar, in the composition (claims)."

However, chicken broth contains not only anserine and carnosine, but creatine, collagen, amino acid and vegetables for flavor. The Office Action does not state that there is a sufficient amount of anserine in chicken broth to provide a muscular fatigue-controlling effect. Although Harris et al. disclosed simple carbohydrates, as discussed above, "ribose" is not specifically mentioned. Accordingly, there are many possible combinations of various sugars and various components in chicken broth. It is respectfully submitted that one having ordinary skill in the art could not predict with any degree of certainty that out of the many combinations encompassed by Harris et al., that applicants' combination of anserine and ribose would provide a synergistic effect.

The above claims 20 and 21 are clearly free of the position taken in the paragraph bridging pages 4 and 5 of the Office

Action, since these claims definitely exclude the ingredients in chicken broth that were not recited in applicants' claims.

In reply to the position set forth in the large full paragraph on page 6 of the final rejection, submitted herewith is a further DECLARATION UNDER 37 CFR 1.132 of Yoshiharu MATAHIRA dated February 16, 2004, which serves to supplement the previously submitted September 30, 2002 MATAHIRA DECLARATION. With respect of Rule 116, consideration of the enclosed February 16, 2004 MATAHIRA DECLARATION is respectfully requested since, as discussed hereinbelow, the enclosed February 16, 2004 MATAHIRA DECLARATION serves to rebut an allegation in the final rejection.

In consideration of comments on page 6, lines 4 to 17 of the Office Action issued September 26, 2003 regarding the previously submitted DECLARATION UNDER 37 CFR 1.132 of Yoshiharu MATAHIRA dated September 30, 2002, the enclosed MATAHIRA DECLARATION provides additional statistical evaluation of the data obtained from ten mice in each group, which verifies the synergistic results exhibited in a simultaneous administration of anserine and D-ribose.

As seen in Fig. 1 of the enclosed DECLARATION UNDER 37 CFR 1.132 of Yoshiharu MATAHIRA dated February 16, 2004, an

annotation for P-values on the top of bars 4, 5 and 8 in the graph has been included, which makes it clear that there is a statistical significance in the difference between the pair of groups of interest, namely bar 4 vs. bar 8 and bar 5 vs. bar 8. By taking account of this, one of ordinary skill in the art would undoubtedly conclude that the simultaneous administration of anserine and D-ribose according to the presently claimed invention is unexpectedly superiorly effective to enable mice to swim for a prolonged period of time.

In addition to the above, since the simultaneous administration of anserine and D-ribose is carried out with a dosage of 100 mg/kg of body weight for each substance, by comparing this to a dosage of 200 mg/kg of body weight applied in the case of either anserine or D-ribose, one of ordinary skill in the art would readily conclude that the superiority of such simultaneous administration of anserine and D-ribose according to the presently claimed invention is not explained by an additive effect resulting from increasing the dosage.

Regarding the comment on page 6, lines 16 to 18 of the Office Action, in view of the present claims which recite a single imidazole compound, namely anserine, the fact that the

enclosed February 16, 2004 MATAHIRA DECLARATION does not involve other imidazole dipeptides is not relevant.

Applicants' presently claimed invention represents the utilization of selected active ingredients, namely anserine and D-ribose, which are potentiated in a synergistically effective manner for attaining superior anti-fatigue activity when administered simultaneously.

It is respectfully submitted that one of ordinary skill in the art could not have been expected to achieve synergistic results with respect of anti-fatigue activity of selected substances (in this case anserine and D-ribose), unless there was a suggestion in the prior art. Both Harris et al. and St. Cyr et al. do not provide such a suggestion.

St. Cyr et al. describe that by administering a pentose, ATP synthesis is accelerated, and the energy useful for mammals can be increased. By the administration of only ribose, the synthesis of ATP can be accelerated, but the consumption rate of ATP cannot be improved. In this regard, in Test Example 2 of the June 25, 2003 MATAHIRA DECLARATION, it was shown that anserine activates the ATPase in muscles and increases the consumption rate of ATP as the energy source.

It is respectfully submitted that one of ordinary skill in the art would not have considered to combine such references. However, for the reasons discussed below, even assuming *arguendo* that such references are combinable, combining the teachings of Harris et al. and St. Cyr et al. would not result in the presently claimed invention.

The phenomenon of the present invention relies upon a totally new and unexpected discovery in the field. Namely, when anserine and ribose are used in combination, not only ATP synthesis is accelerated by ribose, but also the consumption rate of ATP is accelerated by anserine and, as a result, energy can be remarkably increased. None of the fundamental mechanisms for anti-fatigue activities of imidazole related compounds have shown to be related to that of D-ribose. The present invention provides a method and composition to utilize these effects and/or activities derived from anserine and D-ribose in a synergistic way, not in an antagonistic way, to achieve superior anti-fatigue activities.

It is therefore respectfully submitted that the applicants' claimed invention is not rendered obvious over the references, either taken singly or combined in the manner relied upon in the

Office Action, in view of the many distinctions discussed hereinabove. It is moreover submitted that there are no teachings in the references to combine them in such a manner relied upon in the Office Action.

Reconsideration is requested. Allowance is solicited.

If the Examiner has any comments, questions, objections or recommendations, the Examiner is invited to telephone the undersigned at the telephone number given below for prompt action.

Respectfully submitted

A handwritten signature in black ink, appearing to read 'Richard Barth', with a large circular flourish at the end.

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Encs.: (1) PETITION FOR EXTENSION OF TIME
(2) DECLARATION UNDER 37 CFR 1.132
of Yoshiharu MATAHIRA dated February 16, 2004